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Trimethylsilyl Triflate Mediated Chemoselective Condensation of Arylsulfenyl Glycosides

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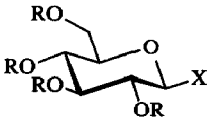
Abstract: Condensation of a fully benzoylated phenylsulfenyl glycoside with either benzylated or benzoylated phenylthio glycosyl acceptors under the agency of trimethylsilyl triflate proceeds with a good degree of chemoselectivity in the presence of the scavenger triethylphosphite.

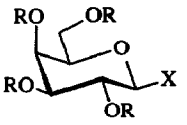
Recently, Roy *et al.*[1] reported that a so-called "latent" 4-nitrophenyl thiosialoside was inert towards the powerful promoters *N*-iodosuccinimide / catalytic triflic acid[2] (NIS/TfOH) and dimethyl (methylthio)sulfonium triflate[3] (DMTST). However, a simple two-step conversion of the electron withdrawing (EW) NO_2 group into the electron donating (ED) NHAc resulted in an "active" glycosyl donor. The potential usefulness of the "latent" nature of the nitro group was nicely illustrated[4] by iodonium ion promoted chemoselective glycosylation of 4-nitrophenyl 1-thio-β-D-glycosides with "armed" or "disarmed" *n*-pentenyl glycosides. Apart from this, it was also established that a partially benzoylated 4-nitrophenyl thioglycoside ("disarmed" acceptor) could be condensed chemoselectively under the influence of DMTST with a fully benzylated 4-nitrophenyl thioglycoside ("armed" donor). In spite of these interesting developments, the application of phenyl thioglycosides gained a new impetus by the finding of Kahne *et al.*[5] that rather inactive nucleophiles can be effectively glycosylated by triflic anhydride mediated activation of phenylsulfenyl glycosyl donors which, in turn, are readily accessible by oxidation (*m*CPBA) of phenyl thioglycosides. More recently[6], it was revealed by the same group that the glycosylation of a phenyl thioglycoside with a phenylsulfenyl glycoside occurs selectively under the influence of triflic acid (TfOH) and in the presence of the scavenger methyl propiolate (MP). The latter finding, together with the fact that the reactivity of phenylsulfenyl donors can be regulated by the introduction of EW or ED groups at the para position of the phenyl ring (reactivity order: OMe > H > NO_2), enabled Kahne *et al.* to assemble a precursor of the ciclamycin 0 trisaccharide in a one-step synthesis.

In order to widen the scope of arylsulfenyl glycosides in sugar chemistry, we report here that trimethylsilyl triflate (TMSOTf) in the presence of triethylphosphite (TEP) is an effective promoter system for the selective activation of phenylsulfenyl glycosides.

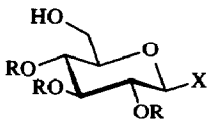
In order to evaluate the effect of the EW nitro group on the reactivity of a 4-nitrophenylsulfenyl donor, we firstly condensed (see Table, entry 1) the fully benzoylated 4-nitrophenylsulfenyl glycoside **2**[7], prepared in 70% yield by oxidation of **1**[8] with *m*CPBA, with the partially benzylated 4-nitrophenylthio glycosyl acceptor **5**[8] under the conditions[6] of Kahne *et al.* (*i.e.* TfOH/MP). Work-up and purification of the reaction mixture gave predominantly the 1,6-anhydro derivative **17** and a negligible amount (<10%) of disaccharide **12**[7]. The formation of the fully benzylated 1,6-anhydro-D-glucose derivative **17** may be rationalized as follows. Reaction of 4-nitrophenylsulfenic acid, generated *in situ* during the activation of donor **2** with TfOH, may be more effective with acceptor **5** than with the scavenger. On the other hand[9], glycosylation of **5** with **2** under Vorbrüggen[10] conditions (*i.e.* TMSOTf) furnished the required dimer **12** in a rather low[11] yield (see entry 2). The rather unsatisfactory outcome of the latter condensation is probably due to the transiently formed 4-nitrophenylsulfenyl



1. X = $SPhNO_2$; R = Bz
2. X = $S(O)PhNO_2$; R = Bz



3. X = SPh; R = Bz
4. X = S(O)Ph; R = Bz

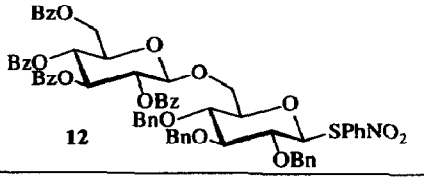
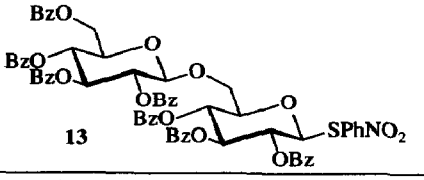
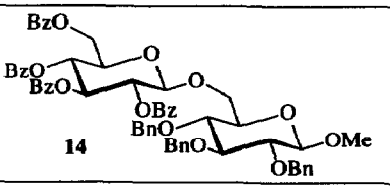
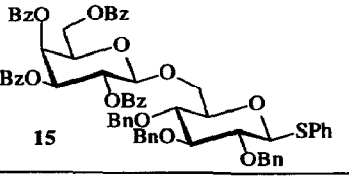
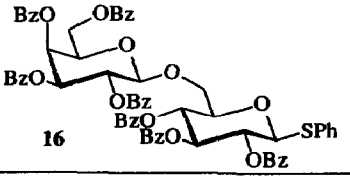
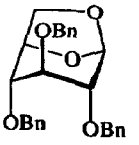
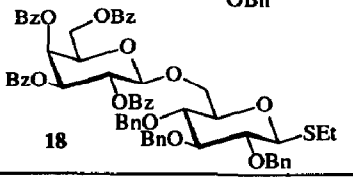


5. X = $SPhNO_2$; R = Bn
6. X = $SPhNO_2$; R = Bz
7. X = OMe; R = Bn
8. X = SEt; R = Bn
9. X = SEt; R = Bz
10. X = SPh; R = Bn
11. X = SPh; R= Bz

trimethylsilyl ester which, in turn, may activate[12] acceptor **5** resulting in the formation of its 1,6-anhydro derivative. It was assumed that the undesired activation by this species could be eliminated by deoxygenation[13] with TEP. However, it is evident from the result in entry 3 that the addition of TEP has no dramatic effect on the yield of **12**. In order to suppress the unwanted cyclization of the acceptor, the two glycosylations in entries 2 and 3 were executed using the corresponding partially benzoylated acceptor **6**[8], which is less prone to cyclization. Indeed, TLC analysis showed in each case the absence of the cyclization product derived from acceptor **6**. In contrast, the use of acceptor **6**, instead of **5**, failed to have a significant effect, either in the absence (entry 4) or presence (entry 5) of TEP, on the yield[14] of disaccharide **13**[7]. The possible activation of an anomeric 4-nitrophenylthio group in the acceptor was corroborated indirectly by the following two experiments. Firstly, glycosylation of the intrinsically inert methyl glycosyl acceptor **7** with donor **2** proceeded smoothly to give dimer **14**[7] in a good yield (entry 6). Secondly, glycosylation of the non-terminal[15] ethylthio glycosyl acceptor **9**, which is compatible[16] with TMSOTf-assisted condensation, with **2** led to an intractable mixture of products. The rather puzzling results obtained thus far urged us to examine the glycosylating properties of the similarly protected phenylsulfenyl donor **4**[7], prepared in 91% yield from **3**, under the influence of TMSOTf. To this end, the partially benzylated phenylthio glycosyl acceptor **10** was glycosylated first (entry 7) with donor **4** in the absence of TEP. TLC analysis of the reaction mixture revealed no detectable formation of dimer **15**[7] (*cf.* entry 2). Execution, however, of the same glycosylation in the presence of TEP[17] gave dimer **15** (entry 8) in an acceptable yield (*cf.* entry 3), thus indicating that the trapping of the *in situ* formed phenylsulfenyl trimethylsilyl ester is rather effective. Furthermore, glycosylation of the partially benzoylated phenylthio glycosyl acceptor **11** (entry 9) in the presence of TEP gave dimer **16**[7] in an excellent yield (*cf.* entry 5). The efficacy of the scavenger is further illustrated by the results of the glycosylation of the partially benzylated ethylthio acceptor **8** with donor **4**. Thus, the omission of TEP led predominantly to the 1,6-anhydro derivative **17** (entry 10). However, the isolation of dimer **18**[7], albeit in a modest yield (entry 11), indicates that the *in situ* generated phenylsulfenyl trimethylsilyl ester reacts more rapidly with TEP than with the anomeric ethylthio group.

In conclusion, the results presented in this paper clearly indicate that TMSOTf in the presence of TEP is a valuable promoter system for the chemoselective glycosylation of phenylsulfenyl donors with phenylthio acceptors. In addition, the effective trapping of a phenylsulfenyl trimethylsilyl ester by TEP, together with the decreased proclivity of an anomeric 4-nitrophenylsulfide towards this reactive species, may open the way to glycosylate a 4-nitrophenylthio acceptor (*e.g.* **6**) in a highly selective manner with a phenylsulfenyl donor (*e.g.* **4**). The reactivity of the resulting dimer (*e.g* **13**) may now be modulated in several ways by transformation of the anomeric 4-nitrophenylsulfide function [*i.e.* oxidation of sulfur and (or) reduction-acetylation of the nitro group].

Table 1. Relevant Data on the Glycosylations of Acceptors 5-8, 10 and 11 with Arylsulfenyl Donors 2 and 4.

Entry	Donor	Acceptor	Promoter	Temp.	Yield	Product[c]
1	**2**	**5**	TfOH MP	-30°C	—	
2	**2**	**5**	TMSOTf	-30°C	43%	
3	**2**	**5**	TMSOTf TEP	-30°C[a]	51%	 **12**
4	**2**	**6**	TMSOTf	-30°C	46%	
5	**2**	**6**	TMSOTf TEP	-30°C[a]	39%	 **13**
6	**2**	**7**	TMSOTf	-30°C	70%	 **14**
7[b]	**4**	**10**	TMSOTf	-60°C	—	
8[b]	**4**	**10**	TMSOTf TEP	-60°C[a]	64%	 **15**
9[b]	**4**	**11**	TMSOTf TEP	-60°C[a]	84%	 **16**
10	**4**	**8**	TMSOTf	0°C	66%	 **17**
11	**4**	**8**	TMSOTf TEP	0°C	38%	 **18**

[a]The mixture was warmed to 20°C. [b]Two equivalents of donor used. [c]Satisfactory elemental analyses were obtained for compounds **12-16** and **18**. The presence of the expected β-linkage in compounds **12-16** and **18** was firmly established[7] by NMR spectroscopy.

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7. Relevant NMR data for compounds **2**, **4**, **12-16** and **18** ($CDCl_3$): **2** (one isomer) ^{13}C δ 93.2 (C-1), ^{1}H δ 4.94 (d, H-1, $J_{1,2}$ 9.8 Hz); (other isomer) ^{13}C δ 90.2 (C-1), ^{1}H δ 4.71 (d, H-1, $J_{1,2}$ 9.5 Hz). **4** (one isomer) ^{13}C δ 92.4 (C-1), ^{1}H δ 4.96 (d, H-1, $J_{1,2}$ 10.0 Hz); (other isomer) ^{13}C δ 89.7 (C-1), ^{1}H δ 4.70 (d, H-1, $J_{1,2}$ 10.0 Hz). **12** ^{13}C δ 86.3 (C-1), 101.2 (C-1'); ^{1}H δ 4.72 (d, H-1, $J_{1,2}$ 9.8 Hz), 4.85 (d, H-1', $J_{1',2'}$ 7.8 Hz). **13** ^{13}C δ 84.7 (C-1), 101.5 (C-1'); ^{1}H δ 4.99 (d, H-1', $J_{1',2'}$ 7.9 Hz), 5.10 (d, H-1, $J_{1,2}$ 10.0 Hz). **14** ^{13}C δ 101.4 (C-1'), 104.5 (C-1); ^{1}H δ 4.42 (d, H-1, $J_{1,2}$ 8.0 Hz), 4.95 (d, H-1', $J_{1',2'}$ 7.7 Hz). **15** ^{13}C δ 87.0 (C-1), 101.1 (C-1'); ^{1}H δ 4.63 (d, H-1, $J_{1,2}$ 9.7 Hz), 4.89 (d, H-1', $J_{1',2'}$ 7.9 Hz). **16** ^{13}C δ 85.6 (C-1), 101.3 (C-1'); ^{1}H δ 4.91 (d, H-1, $J_{1,2}$ 10.0 Hz), 4.97 (d, H-1', $J_{1',2'}$ 7.9 Hz). **18** ^{13}C δ 86.4 (C-1), 101.4 (C-1'); ^{1}H δ 4.40 (d, H-1, $J_{1,2}$ 9.1 Hz), 4.88 (d, H-1', $J_{1',2'}$ 7.9 Hz).
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9. In this respect it is of interest to note that the glycosylation of **5** with **2** under the influence of triflic anhydride (Tf_2O) and collidine is not advisable as activation of **5** by 4-nitrophenylsulfenyl triflate, released in the activation process of **2**, may compete effectively (see Dasgupta *et al.*, *Carbohydr. Res.* **1988**, *177*, C13-C17; *Carbohydr. Res.* **1990**, *202*, 225-238) with the glycosylation.
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11. Recently, Chanteloup *et al.* (*Tetrahedron Lett.* **1992**, *33*, 5347-5350) showed that TMSOTf was a highly effective promoter in the glycosylation of phenylsulfenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside with silylated nucleobases.
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14. In an earlier paper[4a], we established that disaccharide **13** can be prepared in an excellent yield by glycosylation of **6** with the fully benzoylated ethylthio donor **2** (X = SEt) in the presence of NIS/TfOH, thus indicating that the rather poor yields of the glycosylations in entries 4-5 cannot be ascribed to the low reactivity of the acceptor.
15. A terminal acceptor contains, in contrast with a non-terminal one, an anomeric group which cannot be activated *in situ* by a promoter.
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17. Glycosylation procedure: TEP (0.45 mmol) and TMSOTf (0.30 mmol) were added at -60°C to a stirred mixture of donor **4** (0.30 mmol), acceptor **10** (0.15 mmol) and molecular sieves (4Å) in dichloromethane (3 mL) under nitrogen atmosphere. The reaction was gradually warmed to 20°C. The mixture was filtered, taken up in ethyl acetate, washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to small volume. The mixture was applied to a silica gel column. The crude dimer **15** thus obtained was further purified by Sephadex LH-20 gel filtration.

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